

## P. ENT COOPERATION TREA

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C.20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year)

02 August 2000 (02.08.00)

International application No.

PCT/EP99/09284

Applicant's or agent's file reference

PG3606

International filing date (day/month/year)

30 November 1999 (30.11.99)

Priority date (day/month/year)

01 December 1998 (01.12.98)

Applicant

DELANY, Natalie, Samantha et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

30 June 2000 (30.06.00)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Pascal Piriou

Telephone No.: (41-22) 338.83.38

# INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/EP 99/09284

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/705 C12N15/85 C12N5/10 C07K16/28

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                                                                                        | Relevant to claim No.                 |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| X          | CATERINA, M.J. ET AL.: "The capsaicin receptor: a heat-activated ion channel in the pain pathway"<br>NATURE,<br>vol. 389, no. 6653,<br>23 October 1997 (1997-10-23), pages<br>816-824, XP002075020<br>cited in the application<br>abstract<br>page 819; figures 5A,C<br>page 820, column 2, line 13 -page 821,<br>column 1, line 29<br>page 823, column 2, line 13 - line 14<br>page 817, column 2, line 12 -page 820,<br>column 1, line 21<br>page 823, column 2, line 19 -page 824,<br>column 1, line 5 | 1-3,6,9,<br>14-16,<br>45-47           |
| X          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 26                                    |
| A          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 4,5,7,8,<br>10-13,<br>17-25,<br>48-51 |
|            | --/--                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                       |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

11 April 2000

Date of mailing of the international search report

09/05/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Fuchs, U

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 99/09284

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                       | Relevant to claim No.                                                             |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
|            | <p>page 817; figures 2A-C<br/>page 818; figures 3A-F</p> <p>---</p>                                                                                                                                                                                                                                                      |                                                                                   |
| X          | <p>EMBL Database, Heidelberg, FRG<br/>Emest2 accession number AA700891<br/>22 December 1997<br/>Hillier, L. ET AL.: "zj40d01.s1 Soares<br/>fetal liver spleen INFLS S1 Homo sapiens<br/>cDNA clone 452737 3'"<br/>XP002135284<br/>the whole document</p> <p>---</p>                                                      | 6,7                                                                               |
| X          | <p>EMBL Database, Heidelberg, FRG<br/>Emest6 accession number AI089668<br/>19 August 1998<br/>NCI/NINDS-CGAP: "qa10f06.x1 NCI_CGAP_Brn23<br/>Homo sapiens cDNA clone IMAGE:1686371 3'"<br/>XP002135285<br/>the whole document</p> <p>---</p>                                                                             | 6,8                                                                               |
| X          | <p>BIRO, T. ET AL.: "Recent Advances in<br/>Understanding of Vanilloid Receptors: A<br/>Therapeutic Target for Treatment of Pain<br/>and Inflammation in Skin"<br/>JOURNAL OF INVESTIGATIVE DERMATOLOGY<br/>SYMPOSIUM PROCEEDINGS,<br/>vol. 2, no. 1, August 1997 (1997-08),<br/>pages 56-60, XP002075021</p> <p>---</p> | 48,49                                                                             |
| A          | <p>abstract<br/>page 57; table 1<br/>page 58, column 1, line 8 -column 2, line<br/>16</p> <p>---</p>                                                                                                                                                                                                                     | 50,51                                                                             |
| P,X        | <p>WO 99 37675 A (THE REGENTS OF THE<br/>UNIVERSITY OF CALIFORNIA)<br/>29 July 1999 (1999-07-29)</p> <p>---</p> <p>abstract<br/>page 1, line 1 -page 3, line 30<br/>SEQ ID NOS: 33 and 34<br/>page 100 -page 106<br/>page 58 -page 59; claims 1,24-6,8-14,19</p> <p>---</p> <p>-/--</p>                                  | <p>1,2,4,6,<br/>7,9,10,<br/>12,14,<br/>15,23,<br/>24,26,<br/>45,46,<br/>48,50</p> |

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 99/09284

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                | Relevant to claim No.                                                           |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| P, X       | <p>EP 0 943 683 A (SMITHKLINE BEECHAM PLC)<br/>22 September 1999 (1999-09-22)</p> <p>abstract<br/>page 2, line 1 - line 31<br/>SEQ ID NOS: 1 and 2<br/>page 14-16<br/>page 36 -page 37; claims 1-14<br/>-----</p> | <p>1, 2, 4, 6,<br/>7, 9, 10,<br/>12, 14,<br/>15, 23,<br/>24, 26,<br/>45, 46</p> |

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/ 09284

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 27-45  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/EP 99 09284

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 27-45

Claims 27 - 45 refer to a compound which modulates human vanilloid receptor activity without giving a true technical characterization. Moreover, except two compounds already known in the prior art, no such compounds are defined in the application. In consequence, the scopes of said claims are ambiguous and vague, and their subject matter is not sufficiently disclosed and supported (Art. 5 and 6 PCT).

No search can be carried out for such purely speculative claims whose wording is, in fact, a mere recitation of the result to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/EP 99/09284

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s)                   | Publication<br>date                    |
|-------------------------------------------|---------------------|----------------------------------------------|----------------------------------------|
| WO 9937675 A                              | 29-07-1999          | AU 2466799 A<br>AU 9115698 A<br>WO 9909140 A | 09-08-1999<br>08-03-1999<br>25-02-1999 |
| EP 0943683 A                              | 22-09-1999          | JP 11279196 A                                | 12-10-1999                             |


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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                               |                                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Applicant's or agent's file reference<br>PG3606                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |                                              |
| International application No.<br>PCT/EP99/09284                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | International filing date (day/month/year)<br>30/11/1999                                                                      | Priority date (day/month/year)<br>01/12/1998 |
| International Patent Classification (IPC) or national classification and IPC<br>C12N15/12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                               |                                              |
| Applicant<br>Glaxo Group Limited et al.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                               |                                              |
| <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>                                                                                                                                                                                                                                                       |                                                                                                                               |                                              |
| <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"><li>I <input checked="" type="checkbox"/> Basis of the report</li><li>II <input checked="" type="checkbox"/> Priority</li><li>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li><li>IV <input type="checkbox"/> Lack of unity of invention</li><li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li><li>VI <input checked="" type="checkbox"/> Certain documents cited</li><li>VII <input type="checkbox"/> Certain defects in the international application</li><li>VIII <input checked="" type="checkbox"/> Certain observations on the international application</li></ul> |                                                                                                                               |                                              |
| Date of submission of the demand<br><br>30/06/2000                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Date of completion of this report<br><br>19.02.2001                                                                           |                                              |
| Name and mailing address of the international preliminary examining authority:<br><br> European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Authorized officer<br><br>Bladier, C<br><br>Telephone No. +49 89 2399 7306                                                    |                                              |





# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/09284

## I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

### Description, pages:

1-34 as originally filed

### Claims, No.:

1-51 as originally filed

### Drawings, sheets:

1/41-41/41 as originally filed

### Sequence listing part of the description, pages:

1-46, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/09284

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

## II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed.
  - ☐ translation of the earlier application whose priority has been claimed.
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:  
**see separate sheet**

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application.
  - ☒ claims Nos. 27-44.

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP99/09284

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 27-44.

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

|                               |      |        |                             |
|-------------------------------|------|--------|-----------------------------|
| Novelty (N)                   | Yes: | Claims | 4, 5, 12, 13, 23-25, 48-51  |
|                               | No:  | Claims | 1-3, 6-11, 14-22, 26, 45-47 |
| Inventive step (IS)           | Yes: | Claims |                             |
|                               | No:  | Claims | 1-26, 45-51                 |
| Industrial applicability (IA) | Yes: | Claims | 1-26, 45-51                 |
|                               | No:  | Claims |                             |

2. Citations and explanations  
**see separate sheet**

**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**R Item II**

**Priority**

The complete priority document pertaining to the present application was not available at the time of establishing this preliminary opinion. Hence, the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document (01.12.1998). If it later turns out that this is not correct, the intermediate documents cited in the ISR could become relevant to assess whether the claimed subject-matter of the present application satisfies the criteria set forth in Article 33(1) PCT.

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

No examination is carried out for the subject-matter of claims 27-44 since no ISR has been established for those claims (Rule 66.1(e) PCT), due to the fact that their scope is ambiguous and vague and their subject-matter is not sufficiently disclosed and supported (Art. 5 and 6 PCT).

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Cited documents**

Reference is made to the following documents:

- D1: CATERINA, M.J. *et al.*: 'The capsaicin receptor: a heat-activated ion channel in the pain pathway' NATURE, 389(6653), October 1997, p816-824.
- D2: EMBL Database, Heidelberg, FRG Emest2 accession number AA700891 22 December 1997 Hillier, L. *et al.*: 'zj40d01.s1 Soares fetal liver spleen 1NFLS S1 Homo sapiens cDNA clone 452737 3'.
- D3: EMBL Database, Heidelberg, FRG Emest6 accession number AI089668 19 August 1998 NCI/NINDS-CGAP: 'qa10f06.x1 NCI\_CGAP\_Brn23 Homo

sapiens cDNA clone IMAGE:1686371 3'.

D4: BIRO, T. *et al.*: 'Recent Advances in Understanding of Vanilloid Receptors: A Therapeutic Target for Treatment of Pain and Inflammation in Skin' JOURNAL OF INVESTIGATIVE DERMATOLOGY SYMPOSIUM PROCEEDINGS, 2(1), August 1997, p56-60.

## **2. Novelty and inventive step**

- 2.1.** The subject-matter of **claims 1-26 and 45-51** is directed to novel human vanilloid receptors (hVRs), in particular hVR1 and hVR3, nucleotide sequences encoding said hVRs, expression vectors comprising said nucleotide sequences, stable cell lines comprising said expression vectors, methods for producing said hVRs, antibodies specific for said hVRs, a method for identifying compounds which exhibit hVR modulating activity, and said hVRs for use in a method of screening for agents useful in the treatment or prophylaxis of disorders which are responsive to modulation of hVR activity in a human patient.
- 2.2.** Document D1 discloses the cloning and sequencing of rat vanilloid receptor subtype 1 (rVR1) (see page 823 'Methods', 'Expression cloning and DNA analysis'; page 817 'Results', 'Expression cloning of receptor DNA'). According to Figure 21 of the present application, rVR1 shows similarities with hVR1 and hVR3. Thus rVR1 is a variant of a human vanilloid receptor. Furthermore, document D1 discloses the human EST sequence T11251 (see page 819 Figure 5c and page 821 left-hand column, second paragraph) which is also considered as a variant of a human vanilloid receptor since it shows 68% and 49% identity in 57 aa overlap of hVR1 and hVR3, respectively. Consequently, document D1 anticipates the novelty of **claims 1-3, 6-11, 14-22, and 45-47** (Art. 33(2) PCT). In addition, document D1 describes the use of cloned rVR1 in agonist/antagonist screening assays (see page 817, right-hand column 'VR1 and vanilloid receptor pharmacology'). Thus D1 also anticipates the subject-matter of **claim 26** (Art. 33(2) PCT).

It is noted that those novelty objections are due to the fact that:

- the term 'variant' is unclear and encompasses any nucleotide or amino acid sequence sharing similarities to the nucleotide or amino acid sequence of a

human vanilloid receptor (see objection Item VIII point 1).

- the denominations 'hVR1' and 'hVR3' are arbitrary denominations which do not characterised the human vanilloid receptor (see objection Item VIII point 2). Thus, claims referring to hVR1 or hVR3 are considered to refer to any human vanilloid receptor.

- 2.3.** The specific features of claims 4, 5, 12 and 13 are not found in any document of the search report. Consequently the subject-matter of those claims is novel. However it does not comply with the requirements of Article 33(3) PCT since the provision of nucleotide and amino acid sequences of human vanilloid receptors can technically be carried out without the need of any inventive skill when the homologous rat vanilloid receptor is already known from prior art (see D1) and when various human EST sequences showing high degree of similarity to the rat sequence are available (see human EST sequence T11251 in D1 page 819 Figure 5c and page 821 left-hand column, second paragraph; see also the human EST sequences in D2 and D3).

An inventive step could only not be acknowledged for those claims if an unexpected effect of the human vanilloid receptors over the rat receptor could be shown. Such an effect is at present not recognised. Consequently, **claims 4, 5, 12 and 13** are not admissible under Article 33(3) PCT.

- 2.4.** The specific features of claims 23-25, 48-51 are not found in any document of the search report. Consequently the subject-matter of those claims is novel. However it does not comply the requirements of Article 33(3) PCT for the following reasons: the subject-matter of claims 23-25 is regarded as routine methods that would only be allowable in combinaison with a novel and inventive human vanilloid receptor; the subject-matter of claims 48-51 is obvious over D4 since this document suggests the use of vanilloid receptors as a therapeutic target for treatment of disorders responsive to the modulation of hVR activity (see title, Table 1). Consequently, **claims 23-25, 48-51** are not admissible under Article 33(3) PCT.

**Re Item VI**

**Certain documents cited**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/EP99/09284

**Certain published documents (Rule 70.10)**

| Application No<br>Patent No | Publication date<br>(day/month/year) | Filing date<br>(day/month/year) | Priority date (valid claim)<br>(day/month/year) |
|-----------------------------|--------------------------------------|---------------------------------|-------------------------------------------------|
| WO9937675                   | 29.07.1999                           | 22.01.1999                      | 22.01.1998                                      |
| EP0943683                   | 22.09.1999                           | 27.01.1998                      | 10.03.1998                                      |
|                             |                                      |                                 | 20.07.1998                                      |
|                             |                                      |                                 | 03.09.1998                                      |

**Re Item VIII**

**Certain observations on the international application**

1. The term '**variant**' in claims 1-3, 6-8, 14-16, 23-26, 45-48, 50-51 is not sufficiently clear (Art. 6 PCT). It should either be deleted or defined according to the basis found in the description (pages 9-10) and in such a way that it is not anticipated by the rat receptor. For example as follows: 'variants with greater than 90% identity with the sequences provided and which retain the same biological functionality as the receptors encoded by said sequences'.
2. The terms '**hVR1**' and '**hVR3**' are arbitrary designations that have no meaning for a person skilled in the art. Therefore claims referring to hVR1 and hVR3 (claims 2, 3, 7, 8, 15, 16, 24, 25, 46, 47, 50 and 51) should be reformulated including the nucleotide or amino acid sequence of those receptors (Art. 6 PCT).
3. The formulation '**modified** HEK293, CHO, COS, HeLa or BHK cell line' is unclear since HEK293, CHO, COS, HeLa or BHK cell lines are already modified mammalian cell lines and it is not clear which additional modifications have been done (Art. 6 PCT).

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

# PCT

To:  
GLAXO WELLCOME PLC  
Glaxo Wellcome House  
Attn. DOLTON, Peter I  
Berkeley Avenue  
Greenford  
Middlesex UB6 0NN  
UNITED KINGDOM

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

(PCT Rule 44.1)

|                                        |                          |
|----------------------------------------|--------------------------|
| Global Intellectual Property           |                          |
| RECEIVED<br><br>12 MAY 2000<br><br>P/D | INIT<br><br>M1           |
| Date of mailing<br>(day/month/year)    | FILE<br>(day/month/year) |

✓ 09/05/2000

Applicant's or agent's file reference

PG3606

**FOR FURTHER ACTION**

See paragraphs 1 and 4 below

International application No.

PCT/EP 99/09284

International filing date

(day/month/year)

30/11/1999

Applicant

Glaxo Group Limited et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau.

If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Chantal Meyer



## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

|                                                          |                                                                                                                                                         |                                                                |
|----------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| Applicant's or agent's file reference<br><b>PG3606</b>   | <b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |                                                                |
| International application No.<br><b>PCT/EP 99/ 09284</b> | International filing date (day/month/year)<br><b>30/11/1999</b>                                                                                         | (Earliest) Priority Date (day/month/year)<br><b>01/12/1998</b> |
| Applicant<br><br><b>Glaxo Group Limited et al.</b>       |                                                                                                                                                         |                                                                |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

## 4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**HUMAN VANILLOID RECEPTORS AND THEIR USES**

## 5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☒ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

**12a** \_\_\_\_\_

☐ Non of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

EP 99/ 09284

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 27-45  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

## INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

### What documents must/may accompany the amendments?

#### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

**"Statement under article 19(1)" (Rule 46.4)**

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

**It must be in the language in which the international application is to be published.**

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

**Consequence if a demand for international preliminary examination has already been filed**

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

**Consequence with regard to translation of the international application for entry into the national phase**

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/09284

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/705 C12N15/85 C12N5/10 C07K16/28

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                                                                                        | Relevant to claim No.                 |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| X          | CATERINA, M.J. ET AL.: "The capsaicin receptor: a heat-activated ion channel in the pain pathway"<br>NATURE,<br>vol. 389, no. 6653,<br>23 October 1997 (1997-10-23), pages<br>816-824, XP002075020<br>cited in the application<br>abstract<br>page 819; figures 5A,C<br>page 820, column 2, line 13 -page 821,<br>column 1, line 29<br>page 823, column 2, line 13 - line 14<br>page 817, column 2, line 12 -page 820,<br>column 1, line 21<br>page 823, column 2, line 19 -page 824,<br>column 1, line 5 | 1-3,6,9,<br>14-16,<br>45-47           |
| X          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 26                                    |
| A          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 4,5,7,8,<br>10-13,<br>17-25,<br>48-51 |
|            | -/--                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                       |

Hv2



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

11 April 2000

Date of mailing of the international search report

09/05/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Fuchs, U

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 27-45

Claims 27 - 45 refer to a compound which modulates human vanilloid receptor activity without giving a true technical characterization. Moreover, except two compounds already known in the prior art, no such compounds are defined in the application. In consequence, the scopes of said claims are ambiguous and vague, and their subject matter is not sufficiently disclosed and supported (Art. 5 and 6 PCT).

No search can be carried out for such purely speculative claims whose wording is, in fact, a mere recitation of the result to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 99/09284

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                            | Relevant to claim No.                                                |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
|            | <p>page 817; figures 2A-C<br/>page 818; figures 3A-F</p>                                                                                                                                                                                                                                                      |                                                                      |
| X          | <p>EMBL Database, Heidelberg, FRG<br/>Emest2 accession number AA700891<br/>22 December 1997<br/>Hillier, L. ET AL.: "zj40d01.s1 Soares<br/>fetal liver spleen 1NFLS S1 Homo sapiens<br/>cDNA clone 452737 3'"<br/>XP002135284<br/>the whole document</p>                                                      | 6,7                                                                  |
| X          | <p>EMBL Database, Heidelberg, FRG<br/>Emest6 accession number AI089668<br/>19 August 1998<br/>NCI/NINDS-CGAP: "qa10f06.x1 NCI_CGAP_Brn23<br/>Homo sapiens cDNA clone IMAGE:1686371 3'"<br/>XP002135285<br/>the whole document</p>                                                                             | 6,8                                                                  |
| X          | <p>BIRO, T. ET AL.: "Recent Advances in<br/>Understanding of Vanilloid Receptors: A<br/>Therapeutic Target for Treatment of Pain<br/>and Inflammation in Skin"<br/>JOURNAL OF INVESTIGATIVE DERMATOLOGY<br/>SYMPOSIUM PROCEEDINGS,<br/>vol. 2, no. 1, August 1997 (1997-08),<br/>pages 56-60, XP002075021</p> | 48,49                                                                |
| A          | <p>abstract<br/>page 57; table 1<br/>page 58, column 1, line 8 -column 2, line<br/>16</p>                                                                                                                                                                                                                     | 50,51                                                                |
| P,X        | <p>WO 99 37675 A (THE REGENTS OF THE<br/>UNIVERSITY OF CALIFORNIA)<br/>29 July 1999 (1999-07-29)</p> <p>abstract<br/>page 1, line 1 -page 3, line 30<br/>SEQ ID NOS: 33 and 34<br/>page 100 -page 106<br/>page 58 -page 59; claims 1,24-6,8-14,19</p> <p style="text-align: center;">-/--</p>                 | 1,2,4,6,<br>7,9,10,<br>12,14,<br>15,23,<br>24,26,<br>45,46,<br>48,50 |

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/09284

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                      | Relevant to claim No.                                                       |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| P, X       | <p>EP 0 943 683 A (SMITHKLINE BEECHAM PLC)<br/> 22 September 1999 (1999-09-22)</p> <p>abstract<br/> page 2, line 1 - line 31<br/> SEQ ID NOS: 1 and 2<br/> page 14-16<br/> page 36 -page 37; claims 1-14<br/> -----</p> | <p>1,2,4,6,<br/> 7,9,10,<br/> 12,14,<br/> 15,23,<br/> 24,26,<br/> 45,46</p> |



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/09284

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| WO 9937675 A                              | 29-07-1999          | AU 2466799 A               | 09-08-1999          |
|                                           |                     | AU 9115698 A               | 08-03-1999          |
|                                           |                     | WO 9909140 A               | 25-02-1999          |
| EP 0943683 A                              | 22-09-1999          | JP 11279196 A              | 12-10-1999          |

# PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

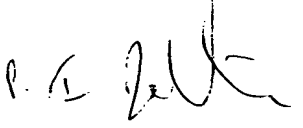
|                                                                                      |              |
|--------------------------------------------------------------------------------------|--------------|
| For receiving Office use only                                                        |              |
| PCT/EP 99 / 09284                                                                    |              |
| International Application No.                                                        |              |
| International Filing Date                                                            | (30. 11. 99) |
| EUROPEAN PATENT OFFICE<br>PCT INTERNATIONAL APPLICATION                              |              |
| Name of receiving Office and "PCT International Application"                         |              |
| Applicant's or agent's file reference<br>(if desired) (12 characters maximum) PG3606 |              |

|                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                               |                                                                                                                                                                                                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Box No. I                                                                                                                                                                                                                                                                                                                                                                                                                                   | TITLE OF INVENTION                                            |                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                             | Novel Receptors                                               |                                                                                                                                                                                                                         |
| Box No. II                                                                                                                                                                                                                                                                                                                                                                                                                                  | APPLICANT                                                     |                                                                                                                                                                                                                         |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below).<br>Glaxo Group Limited<br>Glaxo Wellcome House<br>Berkeley Avenue<br>Greenford, Middlesex, UB6 0NN<br>GB            |                                                               | <input type="checkbox"/> This person is also inventor.<br>Telephone No. 0171 493 4060<br>Facsimile No. 0181 966 8838<br>Teleprinter No. 25456                                                                           |
| State (i.e. country) of nationality: GB                                                                                                                                                                                                                                                                                                                                                                                                     |                                                               | State (i.e. country) of residence: GB                                                                                                                                                                                   |
| This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input checked="" type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box                                                                                                                 |                                                               |                                                                                                                                                                                                                         |
| Box No. III                                                                                                                                                                                                                                                                                                                                                                                                                                 | FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS                 |                                                                                                                                                                                                                         |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)<br>DELANY, Natalie Samantha<br>Glaxo Wellcome plc<br>Gunnels Wood Road<br>Stevenage, Hertfordshire<br>SG1 2NY<br>GB |                                                               | This person is:<br><input type="checkbox"/> applicant only<br><input checked="" type="checkbox"/> applicant and inventor<br><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.) |
| State (i.e. country) of nationality: GB                                                                                                                                                                                                                                                                                                                                                                                                     |                                                               | State (i.e. country) of residence: GB                                                                                                                                                                                   |
| This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box                                                                                                                 |                                                               |                                                                                                                                                                                                                         |
| <input checked="" type="checkbox"/> Further applicants and/or (further) inventors are indicated on a continuation sheet.                                                                                                                                                                                                                                                                                                                    |                                                               |                                                                                                                                                                                                                         |
| Box No. IV                                                                                                                                                                                                                                                                                                                                                                                                                                  | AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE |                                                                                                                                                                                                                         |
| The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: <input checked="" type="checkbox"/> agent <input type="checkbox"/> common representative                                                                                                                                                                                                   |                                                               |                                                                                                                                                                                                                         |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country).<br>DOLTON, Peter I<br>Glaxo Wellcome plc<br>Glaxo Wellcome House, Berkeley Avenue<br>Greenford, Middlesex<br>UB6 0NN<br>GB                                                                                                                                                 |                                                               | Telephone No.: 0171-493-4060<br>Facsimile No.: 0181-966-8838<br>Teleprinter No.: 25456                                                                                                                                  |
| <input type="checkbox"/> Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.                                                                                                                                                                                                                        |                                                               |                                                                                                                                                                                                                         |

| Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS                                                                                                                                                                                                                                                                                                                                                                                                                |  |                                                                                                                                                                                                                                |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <i>If none of the following sub-boxes is used, this sheet is not to be included in the request.</i>                                                                                                                                                                                                                                                                                                                                                                                      |  |                                                                                                                                                                                                                                |  |
| Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i><br><b>SANSEAU, Philippe</b><br><b>Glaxo Wellcome plc</b><br><b>Gunnels Wood Road</b><br><b>Stevenage, Hertfordshire</b><br><b>SG1 2NY</b><br><b>GB</b>    |  | This person is:<br><input type="checkbox"/> applicant only<br><input checked="" type="checkbox"/> applicant and inventor<br><input type="checkbox"/> inventor only <i>(If this check-box is marked, do not fill in below.)</i> |  |
| State (i.e. country) of nationality: <b>FR</b>                                                                                                                                                                                                                                                                                                                                                                                                                                           |  | State (i.e. country) of residence: <b>GB</b>                                                                                                                                                                                   |  |
| This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box                                                                                                                                                              |  |                                                                                                                                                                                                                                |  |
| Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i><br><b>TATE, Simon Nicholas</b><br><b>Glaxo Wellcome plc</b><br><b>Gunnels Wood Road</b><br><b>Stevenage, Hertfordshire</b><br><b>SG1 2NY</b><br><b>GB</b> |  | This person is:<br><input type="checkbox"/> applicant only<br><input checked="" type="checkbox"/> applicant and inventor<br><input type="checkbox"/> inventor only <i>(If this check-box is marked, do not fill in below.)</i> |  |
| State (i.e. country) of nationality: <b>GB</b>                                                                                                                                                                                                                                                                                                                                                                                                                                           |  | State (i.e. country) of residence: <b>GB</b>                                                                                                                                                                                   |  |
| This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box                                                                                                                                                              |  |                                                                                                                                                                                                                                |  |
| Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i><br><br><br><br><br><br><br>                                                                                                                               |  | This person is:<br><input type="checkbox"/> applicant only<br><input type="checkbox"/> applicant and inventor<br><input type="checkbox"/> inventor only <i>(If this check-box is marked, do not fill in below.)</i>            |  |
| State (i.e. country) of nationality:                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  | State (i.e. country) of residence:                                                                                                                                                                                             |  |
| This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box                                                                                                                                                                         |  |                                                                                                                                                                                                                                |  |
| Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i><br><br><br><br><br><br><br>                                                                                                                               |  | This person is:<br><input type="checkbox"/> applicant only<br><input type="checkbox"/> applicant and inventor<br><input type="checkbox"/> inventor only <i>(If this check-box is marked, do not fill in below.)</i>            |  |
| State (i.e. country) of nationality:                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  | State (i.e. country) of residence:                                                                                                                                                                                             |  |
| This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box                                                                                                                                                                         |  |                                                                                                                                                                                                                                |  |
| <input type="checkbox"/> Further applicants and/or (further) inventors are indicated on a continuation sheet.                                                                                                                                                                                                                                                                                                                                                                            |  |                                                                                                                                                                                                                                |  |

| Box No. V                                                                                                                    | DESIGNATION OF STATES                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked): |                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Regional Patent</b>                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                    |
| <input checked="" type="checkbox"/> AP                                                                                       | <b>ARIPO Patent:</b> GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT                                                                                                                                                                                  |
| <input checked="" type="checkbox"/> EA                                                                                       | <b>Eurasian Patent:</b> AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT                                                                                                                      |
| <input checked="" type="checkbox"/> EP                                                                                       | <b>European Patent:</b> AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT               |
| <input checked="" type="checkbox"/> OA                                                                                       | <b>OAPI Patent:</b> BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)..... |
| <b>National Patent</b> (if other kind of protection or treatment desired, specify on dotted line):                           |                                                                                                                                                                                                                                                                                                                                                                                                    |
| <input checked="" type="checkbox"/> AE                                                                                       | United Arab Emirates                                                                                                                                                                                                                                                                                                                                                                               |
| <input checked="" type="checkbox"/> AL                                                                                       | Albania.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> AM                                                                                       | Armenia.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> AT                                                                                       | Austria.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> AU                                                                                       | Australia.....                                                                                                                                                                                                                                                                                                                                                                                     |
| <input checked="" type="checkbox"/> AZ                                                                                       | Azerbaijan.....                                                                                                                                                                                                                                                                                                                                                                                    |
| <input checked="" type="checkbox"/> BA                                                                                       | Bosnia and Herzegovina.....                                                                                                                                                                                                                                                                                                                                                                        |
| <input checked="" type="checkbox"/> BB                                                                                       | Barbados.....                                                                                                                                                                                                                                                                                                                                                                                      |
| <input checked="" type="checkbox"/> BG                                                                                       | Bulgaria.....                                                                                                                                                                                                                                                                                                                                                                                      |
| <input checked="" type="checkbox"/> BR                                                                                       | Brazil.....                                                                                                                                                                                                                                                                                                                                                                                        |
| <input checked="" type="checkbox"/> BY                                                                                       | Belarus.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> CA                                                                                       | Canada.....                                                                                                                                                                                                                                                                                                                                                                                        |
| <input checked="" type="checkbox"/> CH and LI                                                                                | Switzerland and Liechtenstein.....                                                                                                                                                                                                                                                                                                                                                                 |
| <input checked="" type="checkbox"/> CN                                                                                       | China.....                                                                                                                                                                                                                                                                                                                                                                                         |
| <input checked="" type="checkbox"/> CU                                                                                       | Cuba.....                                                                                                                                                                                                                                                                                                                                                                                          |
| <input checked="" type="checkbox"/> CZ                                                                                       | Czech Republic.....                                                                                                                                                                                                                                                                                                                                                                                |
| <input checked="" type="checkbox"/> DE                                                                                       | Germany.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> DK                                                                                       | Denmark.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> EE                                                                                       | Estonia.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> ES                                                                                       | Spain.....                                                                                                                                                                                                                                                                                                                                                                                         |
| <input checked="" type="checkbox"/> FI                                                                                       | Finland.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> GB                                                                                       | United Kingdom.....                                                                                                                                                                                                                                                                                                                                                                                |
| <input checked="" type="checkbox"/> GD                                                                                       | Grenada.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> GE                                                                                       | Georgia.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> GH                                                                                       | Ghana.....                                                                                                                                                                                                                                                                                                                                                                                         |
| <input checked="" type="checkbox"/> GM                                                                                       | Gambia.....                                                                                                                                                                                                                                                                                                                                                                                        |
| <input checked="" type="checkbox"/> HR                                                                                       | Croatia.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> HU                                                                                       | Hungary.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> ID                                                                                       | Indonesia.....                                                                                                                                                                                                                                                                                                                                                                                     |
| <input checked="" type="checkbox"/> IL                                                                                       | Israel.....                                                                                                                                                                                                                                                                                                                                                                                        |
| <input checked="" type="checkbox"/> IN                                                                                       | India.....                                                                                                                                                                                                                                                                                                                                                                                         |
| <input checked="" type="checkbox"/> IS                                                                                       | Iceland.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> JP                                                                                       | Japan.....                                                                                                                                                                                                                                                                                                                                                                                         |
| <input checked="" type="checkbox"/> KE                                                                                       | Kenya.....                                                                                                                                                                                                                                                                                                                                                                                         |
| <input checked="" type="checkbox"/> KG                                                                                       | Kyrgyzstan.....                                                                                                                                                                                                                                                                                                                                                                                    |
| <input checked="" type="checkbox"/> KP                                                                                       | Democratic People's Republic of Korea.....                                                                                                                                                                                                                                                                                                                                                         |
| <input checked="" type="checkbox"/> KR                                                                                       | Republic of Korea.....                                                                                                                                                                                                                                                                                                                                                                             |
| <input checked="" type="checkbox"/> KZ                                                                                       | Kazakhstan.....                                                                                                                                                                                                                                                                                                                                                                                    |
| <input checked="" type="checkbox"/> LC                                                                                       | Saint Lucia.....                                                                                                                                                                                                                                                                                                                                                                                   |
| <input checked="" type="checkbox"/> LK                                                                                       | Sri Lanka.....                                                                                                                                                                                                                                                                                                                                                                                     |
| <input checked="" type="checkbox"/> LR                                                                                       | Liberia.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> LS                                                                                       | Lesotho.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> LT                                                                                       | Lithuania.....                                                                                                                                                                                                                                                                                                                                                                                     |
| <input checked="" type="checkbox"/> LU                                                                                       | Luxembourg.....                                                                                                                                                                                                                                                                                                                                                                                    |
| <input checked="" type="checkbox"/> LV                                                                                       | Latvia.....                                                                                                                                                                                                                                                                                                                                                                                        |
| <input checked="" type="checkbox"/> MD                                                                                       | Republic of Moldova.....                                                                                                                                                                                                                                                                                                                                                                           |
| <input checked="" type="checkbox"/> MG                                                                                       | Madagascar.....                                                                                                                                                                                                                                                                                                                                                                                    |
| <input checked="" type="checkbox"/> MK                                                                                       | The former Yugoslav Republic of Macedonia.....                                                                                                                                                                                                                                                                                                                                                     |
| <input checked="" type="checkbox"/> MN                                                                                       | Mongolia.....                                                                                                                                                                                                                                                                                                                                                                                      |
| <input checked="" type="checkbox"/> MW                                                                                       | Malawi.....                                                                                                                                                                                                                                                                                                                                                                                        |
| <input checked="" type="checkbox"/> MX                                                                                       | Mexico.....                                                                                                                                                                                                                                                                                                                                                                                        |
| <input checked="" type="checkbox"/> NO                                                                                       | Norway.....                                                                                                                                                                                                                                                                                                                                                                                        |
| <input checked="" type="checkbox"/> NZ                                                                                       | New Zealand.....                                                                                                                                                                                                                                                                                                                                                                                   |
| <input checked="" type="checkbox"/> PL                                                                                       | Poland.....                                                                                                                                                                                                                                                                                                                                                                                        |
| <input checked="" type="checkbox"/> PT                                                                                       | Portugal.....                                                                                                                                                                                                                                                                                                                                                                                      |
| <input checked="" type="checkbox"/> RO                                                                                       | Romania.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> RU                                                                                       | Russian Federation.....                                                                                                                                                                                                                                                                                                                                                                            |
| <input checked="" type="checkbox"/> SD                                                                                       | Sudan.....                                                                                                                                                                                                                                                                                                                                                                                         |
| <input checked="" type="checkbox"/> SE                                                                                       | Sweden.....                                                                                                                                                                                                                                                                                                                                                                                        |
| <input checked="" type="checkbox"/> SG                                                                                       | Singapore.....                                                                                                                                                                                                                                                                                                                                                                                     |
| <input checked="" type="checkbox"/> SI                                                                                       | Slovenia.....                                                                                                                                                                                                                                                                                                                                                                                      |
| <input checked="" type="checkbox"/> SK                                                                                       | Slovakia.....                                                                                                                                                                                                                                                                                                                                                                                      |
| <input checked="" type="checkbox"/> SL                                                                                       | Sierra Leone.....                                                                                                                                                                                                                                                                                                                                                                                  |
| <input checked="" type="checkbox"/> TJ                                                                                       | Tajikistan.....                                                                                                                                                                                                                                                                                                                                                                                    |
| <input checked="" type="checkbox"/> TM                                                                                       | Turkmenistan.....                                                                                                                                                                                                                                                                                                                                                                                  |
| <input checked="" type="checkbox"/> TR                                                                                       | Turkey.....                                                                                                                                                                                                                                                                                                                                                                                        |
| <input checked="" type="checkbox"/> TT                                                                                       | Trinidad and Tobago.....                                                                                                                                                                                                                                                                                                                                                                           |
| <input checked="" type="checkbox"/> UA                                                                                       | Ukraine.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> UG                                                                                       | Uganda.....                                                                                                                                                                                                                                                                                                                                                                                        |
| <input checked="" type="checkbox"/> US                                                                                       | United States of America.....                                                                                                                                                                                                                                                                                                                                                                      |
| <input checked="" type="checkbox"/> UZ                                                                                       | Uzbekistan.....                                                                                                                                                                                                                                                                                                                                                                                    |
| <input checked="" type="checkbox"/> VN                                                                                       | Viet Nam.....                                                                                                                                                                                                                                                                                                                                                                                      |
| <input checked="" type="checkbox"/> YU                                                                                       | Yugoslavia.....                                                                                                                                                                                                                                                                                                                                                                                    |
| <input checked="" type="checkbox"/> ZA                                                                                       | South Africa.....                                                                                                                                                                                                                                                                                                                                                                                  |
| <input checked="" type="checkbox"/> ZW                                                                                       | Zimbabwe.....                                                                                                                                                                                                                                                                                                                                                                                      |
| Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet.                 |                                                                                                                                                                                                                                                                                                                                                                                                    |
| <input checked="" type="checkbox"/> CR                                                                                       | Costa Rica.....                                                                                                                                                                                                                                                                                                                                                                                    |
| <input checked="" type="checkbox"/> DM                                                                                       | Dominica.....                                                                                                                                                                                                                                                                                                                                                                                      |
| <input checked="" type="checkbox"/> MA                                                                                       | Morocco.....                                                                                                                                                                                                                                                                                                                                                                                       |
| <input checked="" type="checkbox"/> TZ                                                                                       | Tanzania, <u>United Republic of</u> .....                                                                                                                                                                                                                                                                                                                                                          |

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                        |                                             |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|---------------------------------------------|
| <b>Box No. VI PRIORITY CLAIM</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                               | <input type="checkbox"/> Further priority claims are indicated in the Supplemental Box                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                        |                                             |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                               | Where earlier application is                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                        |                                             |
| Filing Date of Earlier Application (day/month/year)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Number of earlier application | national application: country                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | regional application:* regional Office | international application: receiving Office |
| item (1)<br>01 December 1998<br>(01.12.98)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 9826359.3                     | GB                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                        |                                             |
| item (2)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                        |                                             |
| item (3)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                        |                                             |
| <input type="checkbox"/> The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s):<br>* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box. |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                        |                                             |
| <b>Box No. VII INTERNATIONAL SEARCHING AUTHORITY</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                        |                                             |
| Choice of International Searching Authority (ISA)<br>If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used:<br>ISA/                                                                                                                                                                                                                                                                                                                                                                                                               |                               | Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):<br>Date (day/month/year)      Number      Country (or regional office)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                        |                                             |
| <b>Box. VIII CHECK LIST; LANGUAGE OF FILING</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                        |                                             |
| This international application contains the following number of sheets:<br>request      4<br>description (excluding sequence listing part)      34<br>claims      6<br>abstract      1<br>drawings      41<br>sequence listing part of description      46<br><b>Total number of sheets</b> 132                                                                                                                                                                                                                                                                                                                                                    |                               | This international application is accompanied by the item(s) marked below:<br>1. <input checked="" type="checkbox"/> fee calculation sheet<br>2. <input type="checkbox"/> separate signed power of attorney<br>3. <input type="checkbox"/> copy of general power of attorney; reference number, if any:<br>4. <input type="checkbox"/> statement explaining lack of signature<br>5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s):<br>6. <input type="checkbox"/> translation of international application into (language):<br>7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material<br>8. <input checked="" type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form<br>9. <input type="checkbox"/> other (specify): |                                        |                                             |
| Figure of the drawings which should accompany the abstract:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                               | Language of filing of the international application: <b>English</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                        |                                             |
| <b>Box No. IX SIGNATURE OF APPLICANT OR AGENT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                        |                                             |
| Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                        |                                             |
| <br><b>Peter I Dolton</b><br><b>Agent for the Applicants</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                        |                                             |

|                                                                                                                                             |                                                                                         |                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| For receiving Office use only                                                                                                               |                                                                                         |                                                                                                        |
| 1. Date of actual receipt of the purported international application                                                                        | 30 NOV 1999                                                                             | (30. 11. 99)                                                                                           |
| 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: |                                                                                         | 2. Drawings<br><input checked="" type="checkbox"/> received:<br><input type="checkbox"/> not received: |
| 4. Date of timely receipt of the required corrections under PCT Article 11(2):                                                              |                                                                                         |                                                                                                        |
| 5. International Searching Authority specified by the applicant: ISA/                                                                       | 6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid |                                                                                                        |

|                                                                |                                   |  |
|----------------------------------------------------------------|-----------------------------------|--|
| Date of receipt of the record copy by the International Bureau | For International Bureau use only |  |
| Form PCT/RO/101 (last sheet) (Julv 1998)                       |                                   |  |
| See Notes to the request form                                  |                                   |  |